

## Research Article

# Response to Front and Second Line Treatment in Patients with Acute Non Lymphoblastic Leukemia: A Single Center Experience

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## Abstract

**Background:** Acute Non- Lymphoblastic (ANLL) is the type of leukemia with the worst prognosis. Over the past 30-years, treatment of ANLL consisted of two phases, frontline therapy aimed to achieve leukemic cell clearance, and second line to prevent relapse. This study assessed response to front and second line therapy in patients with ANLL.

**Methods:** Data of 90- ANLL patients were retrospectively collected from hospital records of those who were admitted at the Department of Medical Oncology, South Egypt Cancer Institute (SECI) in the period 2000-2010. Patients were treated with frontline induction regimens, and second line therapy in the form of HAM (33.9%), consolidation for M3 (6.5%). 59.7% of our patients discontinued treatment.

**Results:** 68.9% of patients achieved Complete Remission (CR) that was different among different induction courses. Patients who received HAM, 17 continue remission for a period from 3-18 month till BMT. Those didn't received HAM, 11 patients suffered from relapse. The longest overall (OS) and Disease Free Survival (DFS) were 20 and 18 month in 10.6% and 1.1% respectively. Those who achieved CR after first 1st induction had longer OS and DFS, P <0.05.

**Conclusion:** This study concluded that early blast clearance is a good prognostic factor in ANLL. Also it encouraged post remission therapy with HAM to lengthen DFS till HSCT. However patient incompletion was a problem, accordingly efforts has to be exerted to keep patients in regular treatment.

**Keywords:** ANLL; Frontline therapy; Second line

## Introduction

ANLL is a hematopoietic myeloid stem cell disorder in which the bone marrow is flooded with immature myeloid lineage cells that interfere with the production of normal blood cells [1]. For the past 30 years, and up till now, treatment of ANLL has generally consisted of two phases. The first phase attempts to produce CR and named the induction phase. CR is defined as a bone marrow blasts less than 5% blasts, a neutrophil count greater than 1000, and a platelet count greater than 100 000. CR is the only response that leads to cure and, at the least, to an extension in survival. This can be achieved in about 60–80% of patients with ANLL with intensive chemotherapy regimens, but at least 30% of these patients will develop relapse thereafter. The second phase of therapy aims to prolong the CR. Once a patient has been in remission for 3 years, the likelihood of relapse declines sharply to less than 10% [2].

SECI is a tertiary health center that provides cancer care and treatment to patients with various malignancies at Upper Egypt. A recent study in Upper Egypt found that only 16.3% only of ANLL received consolidation therapy [3]. Another study at Kasr Al Ainy center of clinical oncology and nuclear medicine in the period 2010-2014, showed that the CR of patients with ANLL was 65%, 12.5% early

deaths, 13.8% with refractory disease and the OS was 11.5 months, furthermore half of remittent patients relapsed [4].

As far as we know, this is the first study that assessed response to front and second line treatment in adult patients with ANLL at SECI and addressed clinical challenges of patient management at this big institute.

## Patients and Methods

Data of ANLL patients who were admitted and treated at SECI from 2000 to 2010 were retrospectively collected from patients' files, then arranged and recorded on a new sheet for the study. The extracted data included patients' demographics and ECOG (Eastern Cooperative Oncology Group) performance status. Type of ANLL either by morphology, immunophenotyping and data concerned with drugs used in induction and consolidation were also collected. Particular attention was paid to bone marrow results to document the following: Diagnosis, CR, relapse, and PFS. Unfortunately, cytogenetic and molecular profiles were unavailable for most of the patients thus were omitted. Each record was thoroughly examined to collect the date of death and have the OS. Multiple records of the same patient, who was admitted more than once, were considered as a single record to obtain a full course of the disease.

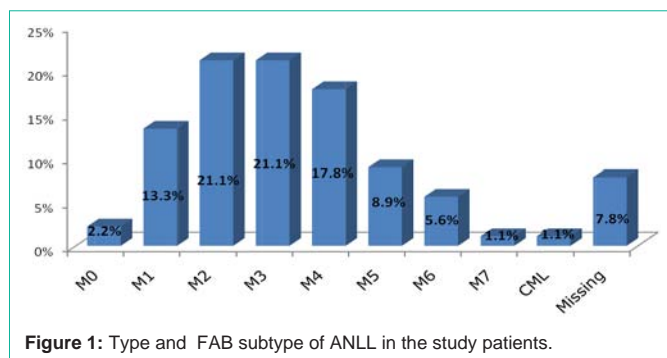


Figure 1: Type and FAB subtype of ANLL in the study patients.

Table 1: Demographic and disease characteristics of 90 patients with ANLL at SECI from 2000– 2010.

| Variable         | Category          | Frequency (%) |
|------------------|-------------------|---------------|
| Age (Mean ± SD)  |                   | 37.9 ± 6.9    |
| Sex              | Male              | 46 (51.1%)    |
|                  | Female            | 44 (48.9%)    |
| Residence        | Assiut            | 44 (48.9%)    |
|                  | Sohag             | 19 (21.1%)    |
|                  | El-Minea          | 4 (4.4%)      |
|                  | Aswan             | 5 (5.6%)      |
|                  | El-Wady           | 1 (1.1%)      |
|                  | Qena              | 8 (8.9%)      |
|                  | Red Sea           | 1 (1.1%)      |
|                  | Missing           | 8 (8.9%)      |
|                  | Performance State | 1             |
| 2                |                   | 14 (15.6%)    |
| TLC              | <100.000          | 86 (95.6%)    |
|                  | >100.000          | 4(4.4%)       |
| CNS infiltration | Yes               | 85(94.4%)     |
|                  | No                | 5(5.6%)       |
| Total number     |                   | 90 (100%)     |

PFS is the time from the start of treatment to the first documentation of objective tumor progression. OS is the time from start of treatment to date of death as a result of any cause or last follow up.

### Statistical Analysis

The collected data were verified, coded then analyzed by using the Statistical Package for Social Sciences (SPSS/PC/VER 17) also a recent version of GraphPad Prism was used. Nevertheless, some records were incomplete others included missing data, accordingly they were excluded. Descriptive statistics: mean, standard deviation, frequencies, percentage were calculated. Kaplan-Mayer and Survival analysis was calculated. Significant test results were considered when P value was < 0.05.

### Ethical Considerations

The study protocol and methods were consistent with the World Medical Association Declaration of Helsinki, also were approved

by the Department of Higher affairs at SECI. Moreover, the study received approval from the Ethics Committee of the Faculty of Medicine, Assiut University. However, as the study was retrospective patient consent was inappropriate. Confidentiality was assured.

## Results

### Demographic and disease characteristics of the study patients

Table 1, showed demographic clinical and disease characteristics of 90 patients with ANLL at SECI from 2000– 2010. The mean age was (37.9±6.9 years), 51.1% were males. Residence ANLL patients at SECI from 2000 – 2010, 44 patients were from Assiut (48.9 %), 19 from Sohag (21.1%), 8 from Qena (8.9 %), 5 from Aswan (5.6 %), 4 from El-Menia (4.4%), 1 patient from El-wady (1.1 %), 1 patient from Red sea governorate (1.1 %), data on residence was missed in 8 patients (8.9 %). ECOG performance status was 1 in 76 patients (84.4 %) and 2 in 14 patients (15.6 %). TLC for the study patients was <100.000 in 86 patients (95.6%) and 4 patients had leukocytic count >100.000 (4.4%). Only 5 patients had CNS infiltration (5.6%).

Figure 1 showed type and subtypes of ANLL, there was 2 patients with M0 (2.2%), 12 patients with M1 (13.3%), 19 patients with M2 by (21.1%),19 with M3 (21.1%), 16 patients with M4 (17.8%), 8 patients with M5 (8.9%), 5 patients with M6 (5.6%), 1 patient with M7 by (1.1%) and 1 patient with CML with blastic transformation (1.1%) (Table 1).

### Response of the study patients to frontline treatment

90 patients received induction, among them 50 (55.5%) patients showed remission after first induction and 40 patients showed no remission. Second induction was given to 16 patients who didn't show remission after first induction, remission occurred in 10 (62%) patients. 2 patients received third induction both of them showed remission, as in (Figure 2). Accordingly response to frontline treatment of ANLL patients at SECI (2000-2010) was CR in 68.9%.

### Response to second line therapy in the study patients

Out of the 62 patients who showed remission 21 patients received HAM regimen (33.9%), among the remaining 4(6.5%) patients diagnosed as M3 and received different consolidation regimens, more than half of the patients (37(59.7%)) discontinue treatment, (Figure 3). Patients who received HAM, 17 patients continue remission for a period ranging from 3 to 18 month till bone marrow transplantation.

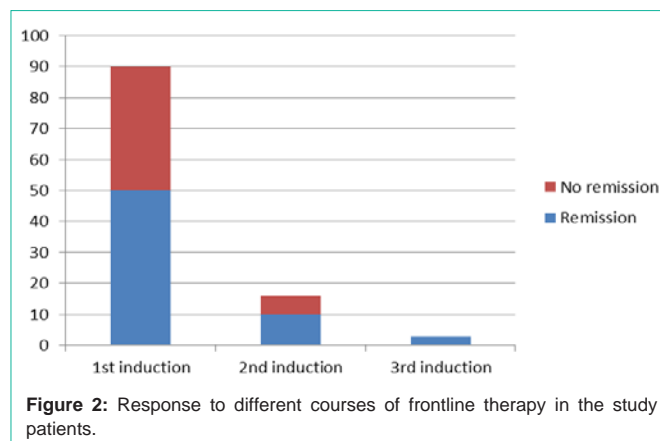
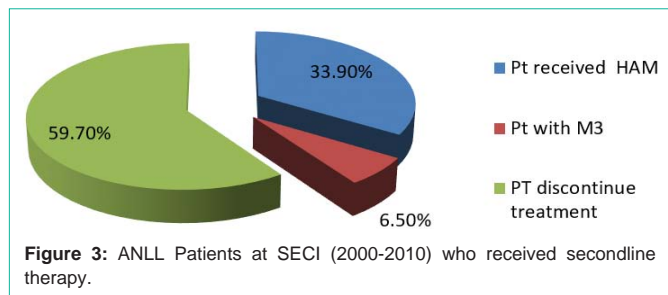


Figure 2: Response to different courses of frontline therapy in the study patients.



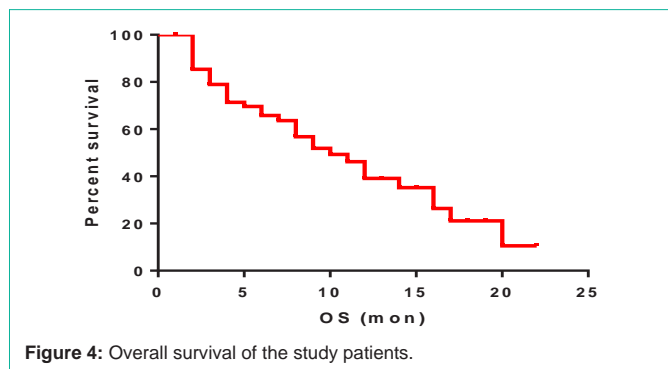
**Figure 3:** ANLL Patients at SECI (2000-2010) who received secondline therapy.

**Table 2:** Overall survival of ANLL patients included in the study.

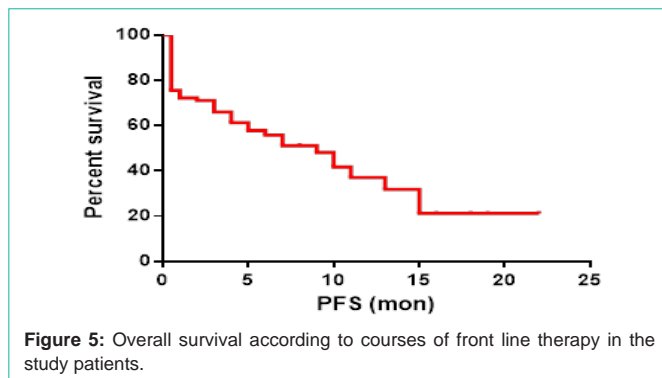
| Survival time (ms) | No. Exposed to Risk | Survival proportion |
|--------------------|---------------------|---------------------|
| 5                  | 42                  | 69.60%              |
| 10                 | 20                  | 49.30%              |
| 15                 | 9                   | 35.20%              |
| 20                 | 2                   | 10.60%              |

**Table 3:** Progression free survival of the study patients.

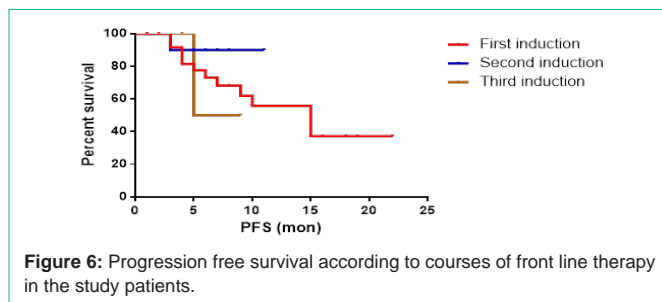
| Survival time | No. Exposed to Risk | Survival proportion |
|---------------|---------------------|---------------------|
| 5             | 35                  | 57.80%              |
| 10            | 15                  | 41.70%              |
| 15            | 6                   | 21.20%              |
| 22            | 1                   | 21.20%              |



**Figure 4:** Overall survival of the study patients.



**Figure 5:** Overall survival according to courses of front line therapy in the study patients.



**Figure 6:** Progression free survival according to courses of front line therapy in the study patients.

While patients who didn't received HAM, 11 patients suffered from relapse (Figure 3).

Assessment of relapse in the study patients showed no relapse in 71(78.8%) patients and relapse in 19 (21.1%) patients. Outcome of ANLL patients, there was 49 patients alive (54.4%) and still under follow up (during the period of the study) and 41 patients died (45.5%).

**Survival analysis of the study patients**

**Overall survival:** In our study the maximum period of follow up was 20 months with survival proportion 10.6%, while half of the patients continue follow up for 10 months, (Table 2 and Figures 4&5).

**Progression free survival of anll:** Median duration without progression of the patients under study is estimated to be 9 months.

**Table 4:** Overall survival according to courses of front line therapy in the study patients.

| Survival time | No. Exposed to Risk       |                           |                           | Survival proportion       |                           |                           |
|---------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|
|               | 1 <sup>st</sup> induction | 2 <sup>nd</sup> induction | 3 <sup>rd</sup> induction | 1 <sup>st</sup> induction | 2 <sup>nd</sup> induction | 3 <sup>rd</sup> induction |
| 5             | 26                        | 8                         | 3                         | 91.3%                     | 100%                      | 100%                      |
| 10            | 14                        | 2                         | 2                         | 72.5%                     | 27.8%                     | 66.6%                     |
| 15            | 8                         | 1                         | 0                         | 64.4%                     | 27.8%                     | 0%                        |
| 20            | 2                         | 0                         | 0                         | 23%                       | 0%                        | 0%                        |

**Table 5:** Progression free survival according to courses of front line therapy in the study patients.

| Survival time | No. Exposed to Risk       |                           |                           | Survival proportion       |                           |                           |
|---------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|
|               | 1 <sup>st</sup> induction | 2 <sup>nd</sup> induction | 3 <sup>rd</sup> induction | 1 <sup>st</sup> induction | 2 <sup>nd</sup> induction | 3 <sup>rd</sup> induction |
| 5             | 21                        | 7                         | 2                         | 77.6                      | 90%                       | 50%                       |
| 10            | 10                        | 1                         | 1                         | 55.8                      | 90%                       | 50%                       |
| 15            | 6                         | 0                         | 0                         | 37.2                      | 0%                        | 0%                        |
| 22            | 1                         | 0                         | 0                         | 37.2                      | 0%                        | 0%                        |

As the courses of treatment spent around 6 months (2 inductions and 3 consolidation) this means that half of patients suffer from relapse within 4 months. Only 1 patient remained without relapse for around one and half year, (Table 3, Figure 7).

**Survival analysis according to courses of front line therapy in the studied sample:** There was no statistically significant difference between courses of front line therapy in OS however patients who showed remission after first induction had a trend for longer survival duration (median survival =16 month), (Table 4 and Figure 6).

As described above similar trend was seen in progression free survival with median survival after first induction was 15 months, P value =0.5, (Table 5 and Figure 7).

## Discussion

ANLL is the most common type of leukemia in adults, yet continues to have the lowest survival rate of all leukemia's [5]. Regarding the Arab world, Statistics have shown that leukemia is one of the 10 most common malignancies in Egypt and many other Arabic countries [6]. It is estimated that there are around 3,335 new cases per year in Egypt [7]. The conventional treatment of ANLL, in many centers worldwide, consisted of front line and second line therapy [8]. In our study we tried to assess the response to these therapies in ANLL cases treated at SECE and their implication on patient survival. Accordingly, we retrospectively collected data of 90-patients with ANLL who were admitted at SECI in the period 2000-2010.

Analysis of the collected data showed male predominance percentage, ANLL in adults has a slight male predominance in most countries. The incidence rate of U.S. males is substantially higher than the incidence rates reported for males in all other countries. The exact significance of this gender preference is not clear [9,10].

In our study, the most common FAB subtypes were M2 (21.1%) and M4 (17.8%). This is the same reported with FAB classification in USA and UK, [11] but M3(21.1%) is also high as SECI is the tertiary referral center at Upper Egypt which has the facilities to treat this type but the other types can be managed in other centers.

ANLL influences all ages but is mainly a disease of the elderly with a median age of 69 years in the white US population, but in our study the median age was 37 years. This median age was albeit consistent with Khaled et al., [3]. The life expectancy of Egyptians is 72 years compared to 78 years for the Americans and almost 95% of the Egyptians are below 60 years compared to 13% for the Americans [12]. So usually at SECI the number of young patients is more than the old patients, and usually young adults seek medical advice more than the elderly. Furthermore, younger adults may be exposed to hazardous chemicals (benzene) or to radiation [13].

Patients who show remission after first induction course survive for a longer duration without relapse than those showing remission for the first time after the second or third induction. Early response to chemotherapy has a major prognostic impact in patients with ANLL. Failure to achieve early blast clearance remains a poor prognostic factor even after early salvage [14].

More recently, long-term results of the multicenter prospective

LAM-2001 trial by the GOELAMS study group showed that Patients with fewer than 5% blasts measured on the 15<sup>th</sup> day after treatment (d15-blasts) had a higher complete response rate (91.7% vs. 69.2%; P<0.0001) and a lower induction death rate (1.8% vs. 6.8%; P=0.001). Five-year event-free (48.4% vs. 25%; P<0.0001), relapse-free (52.7% vs. 36.9%; P=0.0016) and overall survival (55.3% vs. 36.5%; P<0.0001) were significantly higher in patients with d15-blasts lower than 5%. Multivariate analyses identified d15-blasts and cytogenetic risk as independent prognostic factors for the three end points [15].

In the current study the CR of ANLL patients was 68% which was consistent with the reported CR in many studies that ranged from 65-70%, 25% of those could survive more than 3-years [16-18].

Many studies concluded the importance of cytogenetic and molecular analyses in treatment decision for ANLL patients [16,19-22], however this was not available for all patients at the time of this study. According to treatment policy in SECI ANLL patients who show remission after induction are planned to receive consolidation regimen in the form of High Dose Cytarabine (HAM). Only one third of patients who showed remission after induction received HAM. Due to false sensation of complete cure and lack of desire to receive more chemotherapy many of our patients discontinued treatment. Patients who received HAM can survive for a longer duration till bone marrow transplantation can be done for them as long as 18 months.

According to cooperative group MRC16, SWOG/ECOG19 and CALGB23, risk stratification of karyotype abnormalities in patients of ANLL after first remission (CR1), is used to determine post remission treatment. Treatment of choice for unfavorable risk group is allogeneic HSCT [19]. In such case there is no need for further consolidation chemotherapy which is lengthy, toxic and not effective in this group of patients. Applying this risk stratification policy in our management protocol for ANLL may be of benefit for a group of patients who discontinued or cannot withstand further chemotherapy [23,24].

In Egypt facilities that can provide bone marrow transplantation is very limited. In general, ANLL patients should wait from 6 to 12 month or even more for transplantation. Therefore, consolidation treatment is required for such patients to provide relapse free duration as long as possible till they can do bone marrow transplantation, provided good selection of candidate as described above.

## Conclusion

In conclusion this study showed that early remission after first course of front line therapy carried better prognosis in ANLL patients who show remission after second and third course. Moreover, it revealed that consolidation treatment provided a longer duration without relapse, while waiting for bone marrow transplantation. Nevertheless, cytogenetic profile and risk stratification are crucial for directing post remission management of ANLL.

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